REMARKS

It is respectfully requested that the Examiner enter and consider Claims 1 to 8, and 10 to 13 in the version set forth in Appendix II attached to this paper. Accordingly, Claim 9 has been canceled, Claims 1 to 8 have been amended, and Claims 10 to 13 have been added, as indicated in the marked-up version set forth in the Listing of Claims in Appendix I.

Accordingly, Claim 1 has been amended to better bring out that the excipient is in form of a free-flowing powder as disclosed on page 4, indicated lines 20 and 21, of the application, and have added to requirement that the surface-active substance constitute from 10 to 50% by weight of the excipient as disclosed on page 2, indicated line 11, of the application. Additionally, applicants have replaced the expression *"comprising"* by -consisting essentially of- to better distinguish the excipient from dosage forms which contain active ingredients. Further, applicants have introduced the process measures set forth in Claims 8 and 9 as additional product by process features characterizing the excipient.

In light of the changes in Claim 1, Claim 5 has been amended to refer to a content of from 15 to 40% by weight of the surface-active substance in the excipient. The respective range is supported by applicants' disclosure on page 2, indicated line 12, of the application. The subject matter of Claim 9 has been introduced into Claim 8 as an alternative corresponding to the product by process features added to Claim 1.

Additionally, some editorial changes were made in the language of Claims 2, 3, 6 and 7. New Claims 10 to 13 have been added to further bring out some of the subsidiary embodiments of the excipient. The respective features of the excipient are addressed in applicants' disclosure on page 2, indicated line 12, page 4, indicated lines 20 and 21, and indicated lines 13 to 18, and page 2, indicated lines 23 and 24, respectively. No new matter has been added.

The Examiner has maintained the rejection of applicants' claims under Sections 102(b) and 103(a) based on the teaching of ***Davis et al.*** **(US 5,670,158)**, ***Lippmann et al.*** **(US 4,259,315)**, ***Straub et al.*** **(US 5,853,698)**, and ***Bar-Shalom et al.*** **(US 5,618,560)** stating that appli-

cants' previous arguments are, inter alia, based on features which are not recited in the claims, and that applicants' claims allow for the presence of other unrecited ingredients due to the language *"comprising"*. Accordingly, applicants' have amended the claims to refer to an excipient which consists essentially of the recited constituents and to recite the features addressed in applicants' previous argument. The Examiner's position that the subject matter defined in applicants' claims is anticipated by either one of the named references, and is rendered *prima facie* obvious by a combination of the references is therefore no longer deemed applicable.

CONCERNING THE SECTION 102(B) REJECTIONS:

To constitute anticipation, all material elements of the invention as claimed must be found in one prior art source[1]. In light of applicants' amendment the material elements of the invention as claimed include the requirements

(a) that the excipient consists essentially of the polymer and the surface-active substance;

(b) that the surface-active substance is present in the excipient in from 10 to 50% by weight;

(c) that the surface-active substance is liquid or semisolid;

(d) that the excipient is in form of a free-flowing powder; and

(e) that the excipient is obtained by a process which comprises

- spray-drying a solution of the polymer and the surface-active substance, or
- processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt, and subsequently converting the melt into the free-flowing powder

(ie. Claim 1; Claims 2 to 8 and 10 to 13 incorporate the respective requirements by reference to Claim 1).

The disclosure of ***Davis et al.*** relates to a pharmaceutical dosage form comprising bisacodyl as an active ingredient which comprises as essential components

1) rapidly-dissolving bisacodyl means, and

---

1) ie. In re Marshall 577 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Kalm 378 F.2d 959, 154 USPQ 10 (CCPA 1967)

2) delivery means,

(*ie. Abstract, col. 2, indicated line 57, to col. 3, indicated line4, of* **US 5,670,158**). The rapidly-dissolving bisacodyl means are *inter alia* solid dispersions of solid bisacodyl in a water-soluble carrier which are incorporated into the dosage form as solid particulates (*col. 4, indicated lines 36 to 61, of* **US 5,670,158**). The respective embodiment of ***Davis et al.***'s bisacodyl means differs from applicants' excipients in the presence of the active ingredient, and in the absence of a surface active substance. ***Davis et al.*** further state that the bisacodyl means in form of solid particulates may be blended with various excipients which include polymeric excipients (*ie. col. 6, indicated lines 27 to 48, of* **US 5,670,158**) without, however, particularly pointing to or mentioning surface active compounds.

In other embodiments of the bisacodyl means, the bisacodyl is in solution (*col. 4, indicated line 62, to col. 5, indicated line 9, of* **US 5,670,158**). Additionally, ***Davis et al.*** provide that preferably all of the bisacodyl in the dosage forms is incorporated in lipid solutions (*col. 5, indicated line 10 et seq., of* **US 5,670,158**).

The disclosure of ***Davis et al.*** therefore fails to teach or suggest the particular combination of material elements which characterizes applicants' excipient.

The disclosure of ***Lippmann et al.*** relates to gelatine capsules containing a controlled release form wherein a potassium salt constitutes the active ingredient (*ie. Abstract, col. 2, indicated lines 40 to 51, of* **US 4,259,315**). The only free-flowing powder which is mentioned by ***Lippmann et al.*** is obtained by coating the potassium salt with a pharmaceutically acceptable polymeric material (*col. 3, indicated line 53, to col. 4, indicated line 7, of* **US 4,259,315**). The respective powder differs from applicants' excipients in the presence of the active ingredient, and in the absence of a surface active substance. In accordance with the teaching of ***Lippmann et al.*** the microcapsules are subsequently blended with surfactants in amounts of from 0.05 to 5% by weight (*col. 4, indicated lines 55 to 63, of* **US 4,259,315**). The disclosure of ***Lippmann et al.*** therefore fails to teach or suggest the particular combination of material elements which characterizes applicants' excipient.

The disclosure of ***Straub et al.*** relates to polymeric microparticles which contain a fluorinated gas to enhance echogenicity (*Abstract, col. 5, indicated lines 14 to 23, of* **US 5,853,698**)[2]. ***Straub et al.*** further mention that *"surfactants may be added during the synthesis of the ... microparticles"* and that, at that point, the surfactants are used in 0.1 to 5% by weight[3]. The respective microparticles differ from applicants' excipients in the presence of the fluorinated gas, and if not in the absence of a surface active substance then in the amount of the surface-active substance relative based on the combined weight of the polymer and the surfactant. The disclosure of ***Straub et al.*** therefore fails to teach or suggest the particular combination of material elements which characterizes applicants' excipient.

The disclosure of ***Bar-Shalom et al.*** is not concerned with flowable powders but relates to a shaped article formed from a combination of a crystalline polymer, a non-ionic emulsifier and an active ingredient. The respective disclosure therefore also fails to teach or suggest the particular combination of material elements which characterizes applicants' excipient.

Neither one of the teachings relied upon by the Examiner in the rejection under Section 102(b) show all of the elements of applicants' invention in the particular combination in which they are found in accordance with applicants' claims. The references therefore cannot be taken as anticipating within the meaning of Section 102(b). Withdrawal of the Examiner's rejection under Section 102(b) is therefore respectfully solicited.

CONCERNING THE SECTION 103(A) REJECTION:

Three basic criteria have to be met in order to establish a *prima facie* case of obviousness:

(1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one

---

2) The Examiner will note that ***Straub et al.*** point out in lines 14 to 16 of that section that the system *consists* of the polymer and the fluorinated gas.

3) The Examiner will note that ***Straub et al.*** does not disclose on which basis the weight percentage of the surfactant is to be measured.

of ordinary skill in the art, to modify the reference or to combine the reference teachings[4],

(2) there must be a reasonable expectation of success, and

(3) the prior art reference or the combined references must teach or suggest all of the claim limitations.

Additionally, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and cannot be based on applicants' disclosure[5]. Also, the level of skill in the art cannot be relied upon to provide the suggestion to combine references[6].

Applicants' invention as defined in Claim 1 resides in a free flowing powder consisting essentially of a polymer and a surface-active substance which is liquid or semisolid. It is inherent in the requirement that the excipient is in form of a free flowing powder that the liquid or semisolid surface-active substance which constitutes from 10 to 50% by weight of the excipient is, due to the particular measures taken in the preparation of the excipient, adsorbed into the polymer rather than merely forming a "coating" on the surface of polymer particles.

The teaching of ***Davis et al.*** does not suggest or imply a combination of a surface-active ingredient with a polymeric carrier *without* the addition of the active ingredient bisacodyl. Even with regard to the bisacodyl containing preparations, ***Davis et al.*** fail to suggest or imply compositions which comprise a surface active substance as well as a polymeric carrier. In their teaching, ***Davis et al.*** distinguish between *solid* bisacodyl means[7] which comprise polymeric constituents but no surface active component, and *liquid* bisacodyl means[8] which comprise surfactants but no polymeric constituent.

---

4) There are three possible sources for motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of a person of ordinary skill in the art. In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-1458 (CAFC 1998)

5) In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438, 1442 (CAFC 1991)

6) Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161, 1171 (CAFC 1999)

7) Such solids are specifically addressed in col. 4, indicated lines 36 to 61, and col. 6, indicated lines 26 to 48, of ***US 5,670,158***.

8) Such liquids are specifically addressed in col. 4, indicated line 62, to col. 5, indicated line 20, and col. 6, indicated lines 49 to 54, of ***US 5,670,158***.

The teaching of ***Lippmann et al.*** provides that a hydrophilic surfactant is applied to the surface of the encapsulated potassium salts, and combinations of a surfactants and polymers without an active component are neither suggested nor implied. Also, where the surfactant is combined with the microcapsules, the teaching of ***Lippmann et al.*** does not suggest or imply an adsorption of the surfactant into the polymer, particularly since such an adsorption would defeat the purpose which the surfactant has in the context of ***Lippmann et al.***'s dosage form, ie. increasing the flowability of the wetted microcapsules upon administration to humans[9)].

The combined teachings of ***Davis et al.*** and ***Lippmann et al.*** therefore fall short from rendering applicants' invention obvious under the provisions of Section 103(a).

Even if the teaching of ***Straub et al.*** is included into the combination of teachings, the result remains the same. Although ***Straub et al.*** disclose that surfactants may be added during the synthesis of the microparticles to stabilize micro-bubbles generated prior to spray drying, ***Straub et al.*** also teaches that the microparticles consist of the polymer particles and the encapsulated gases[10)]. A person of ordinary skill in the art is therefore not apprised by the teachings of ***Davis et al.***, ***Lippmann et al.*** and ***Straub et al.*** that the particular measures which characterize the manufacture of applicants' excipient will provide for a free flowing powder wherein a liquid or semisolid surface-active substance is adsorbed into a polymer. The Examiner will also note that neither ***Davis et al.*** nor ***Straub et al.*** or ***Lippmann et al.*** teach or suggest a combination wherein the surfactant constitutes 10 to 50% by weight of the weight of polymer and surfactant.

The teaching of ***Bar-Shalom et al.*** relates to a shaped article formed by melt extrusion of a mixture comprising, in addition to an active ingredient, a polymer and a surfactant rather than a particulate form such as a free-flowing powder. Additionally, the shaped article addressed by ***Bar-Shalom et al.*** is coated, and no information is provided on the physical properties of the surface of the melt extruded article which would convey to a person of ordinary skill that it is possible to convert such a shaped article into a free

9) The purpose is explained by ***Lippmann et al.*** in col. 5, indicated lines 37 to 47, and in col. 2, indicated line 55, to col. 3, indicated line 5, of ***US 4,259,315***.

10) Note the statements of ***Straub et al.*** in col. 9, indicated lines 19 to 21, and in col. 5, indicated lines 14 to 17, of ***US 5,853,698***.

flowing powder. Since the respective information cannot be derived from the teachings of ***Davis et al.***, ***Lippmann et al.*** and/or ***Straub et al.*** a combination of ***Bar-Shalom et al.***'s teaching with the disclosure of the referenced art is insufficient to arrive at applicants' invention. The respective references therefore cannot be considered to render the subject matter of applicants' claims obvious within the meaning of Section 103(a). Favorable reconsideration of the Examiner's position and withdrawal of the respective rejection is therefore respectfully solicited.

REQUEST FOR EXTENSION OF TIME:

It is respectfully requested that a *one* month extension of time be granted in this case. A check for the *$110.00* fee is attached.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11.0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
KEIL & WEINKAUF

/HBKeil

Herbert B. Keil
Reg. No. 18,967

1350 Connecticut Ave, N.W.
Washington, D.C. 20036
(202) 659-0100

Encl.: THE LISTING OF CLAIMS (Appendix I)
THE AMENDED CLAIMS (Appendix II)

HBK/BAS

APPENDIX I:

THE LISTING OF CLAIMS (version with markings, showing the changes made):

1. (*currently amended*) An excipient [~~in powder form~~] adapted for use in a solid pharmaceutical [~~presentations~~] dosage form, wherein said excipient is in form of a free-flowing powder and consists essentially of [~~comprising~~] a pharmaceutically acceptable polymer and from 10 to 50% by weight, based on the total weight of said excipient, of a liquid or semisolid solubilizing surface-active substance, and wherein said excipient is obtained either

   by a process which comprises spray-drying a solution of the polymer and the surface-active substance, or

   by a process which comprises processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt, and subsequently converting the melt into the free-flowing powder.

2. (*currently amended*) [~~An~~] The excipient [~~as claimed~~] defined in claim 1, comprising a surface-active substance [~~with~~] which has a drop point in the range from 20 to 40°C.

3. (*currently amended*) [~~An~~] The excipient [~~as claimed~~] defined in claim 1, comprising a surface-active substance [~~with~~] which has an HLB of from 10 to 15.

4. (*currently amended*) [~~An~~] The excipient [~~as claimed~~] defined in claim 1, [~~comprising as pharmaceutically acceptable~~] wherein the polymer is a homo- or copolymer of N-vinylpyrrolidone.

5. (*currently amended*) [~~An~~] The excipient [~~as claimed~~] defined in claim 1, comprising [~~more than 10 and up to 70%~~] from 15 to 40% by weight of the surface-active substance.

6. (*currently amended*) [~~An~~] The excipient [~~as claimed~~] defined in claim 1, comprising ethoxylated sorbitan fatty acid esters as surface-active substances.

7. (*currently amended*) [~~An~~] The excipient [~~as claimed~~] defined in claim 1, comprising products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface-active substance.

8. (*currently amended*) A process for producing [~~excipients in powder form as claimed~~] the excipient defined in claim 1, which comprises ei-

ther spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer, or processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder.

9. (*canceled*) ~~A process for producing excipients as claimed in claim 1, which comprises processing the constituents to a homogeneous melt in an extruder, followed by shaping.~~

10. (*new*) The excipient defined in claim 1, comprising from 20 to 30% by weight of the surface-active substance.

11. (*new*) The excipient defined in claim 1, in form of a free-flowing powder of particles having a particle size of from 10 to 1000 μ.

12. (*new*) The excipient defined in claim 1, consisting of the polymer and the surface-active substance and optionally one or more ingredients selected from the group consisting of flow regulators, dyes, mold release agents, fats, waxes, disintegrants, bulking agents and other conventional tableting excipients.

13. (*new*) The excipient defined in claim 1, wherein the surface-active substance is a non-ionic compound.

APPENDIX II:

THE AMENDED CLAIMS (clean version of *all* claims):

1. (*currently amended*) An excipient adapted for use in a solid pharmaceutical dosage form, wherein said excipient is in form of a free-flowing powder and consists essentially of a pharmaceutically acceptable polymer and from 10 to 50% by weight, based on the total weight of said excipient, of a liquid or semisolid solubilizing surface-active substance, and wherein said excipient is obtained either

   by a process which comprises spray-drying a solution of the polymer and the surface-active substance, or

   by a process which comprises processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt, and subsequently converting the melt into the free-flowing powder.

2. (*currently amended*) The excipient defined in claim 1, comprising a surface-active substance which has a drop point in the range from 20 to 40°C.

3. (*currently amended*) The excipient defined in claim 1, comprising a surface-active substance which has an HLB of from 10 to 15.

4. (*currently amended*) The excipient defined in claim 1, wherein the polymer is a homo- or copolymer of N-vinylpyrrolidone.

5. (*currently amended*) The excipient defined in claim 1, comprising from 15 to 40% by weight of the surface-active substance.

6. (*currently amended*) The excipient defined in claim 1, comprising ethoxylated sorbitan fatty acid esters as surface-active substances.

7. (*currently amended*) The excipient defined in claim 1, comprising products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface-active substance.

8. (*currently amended*) A process for producing the excipient defined in claim 1, which comprises either spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer, or processing the polymer and the surface-active

substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder.

9. (*canceled*)

10. (*new*) The excipient defined in claim 1, comprising from 20 to 30% by weight of the surface-active substance.

11. (*new*) The excipient defined in claim 1, in form of a free-flowing powder of particles having a particle size of from 10 to 1000 μ.

12. (*new*) The excipient defined in claim 1, consisting of the polymer and the surface-active substance and optionally one or more ingredients selected from the group consisting of flow regulators, dyes, mold release agents, fats, waxes, disintegrants, bulking agents and other conventional tableting excipients.

13. (*new*) The excipient defined in claim 1, wherein the surface-active substance is a non-ionic compound.